REMARKS

Claims 1-43 are pending in this application.

Claims 3, 5-16, 17 and 25-43 are withdrawn. Applicant timely traversed the restriction (election) requirement in the reply filed on 3/22/2007. Claim 17 has been determined by the Examiner as withdrawn from prosecution. Claim 24 recites a number of conditions that can be considered to be acute inflammatory lung diseases, such as asthma, allergic bronchitis and reactive airway disease syndrome, and so is being examined as drawn to the elected species.

Claims 1, 2, 4, and 18-24 are under consideration as drawn to FoxA2 protein, treatment of acute inflammatory lung disease.

Specification

The Examiner contends that the title of the invention is not descriptive and that a new title is required that is clearly indicative of the invention to which the claims are directed. Applicants believe the title is descriptive but invite the Examiner to suggest an alternative title she believes is more descriptive.

Claim Objections

Claim 4 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant has now amended claim 4.

Claim 1 is objected to for encompassing non-elected inventions. Appropriate correction will be made if required upon the close of prosecution.

Claim Rejections - 35 USC § 112, second paragraph

The Examiner has rejected claims 1, 2, 4 and 17-24 under 35 U.S.C. 112, second paragraph. The Examiner contends that claim 1 is indefinite as the metes and bounds of the term "FoxA2 therapeutic" cannot be determined. Applicant has now amended claim to limit the therapeutic to FoxA2 protein.

The Examiner contends that claim 18 is indefinite as the term "acute inflammatory lung disease" does not have a recognized meaning in the art, nor is it defined by the specification, such that the Examiner cannot determine the metes and bounds of the claim. Claim 18 has been amended to provide for "inflammatory lung disease". The term "inflammatory lung disease" is well known in the art and refers to a disease associated with an inflammatory or immune response in the lung. Exemplary inflammatory lung diseases include, for example, asthma, acute lung injury, adult respiratory distress syndrome, emphysema, bronchitis, cystic fibrosis, and interstitial lung disease such as interstitial pneumonitis, idiopathic fibrosis and interstitial fibrosis.

The Examiner contends that claim 19 is indefinite; the claim states that the FoxA2 therapeutic agent decreases lung inflammation; it is not clear that this constitutes a further method step, and if so, what that further method step is. Claim 19 has now been amended to clarify that the FoxA2 therapeutic agent is administered in an amount and duration sufficient to decrease lung inflammation in the mammal.

The Examiner contends that claim 20 is indefinite for stating "a" mammal; the dosage should be relative to the particular mammal being treated. As written, it is not clear what mammal's weight is to be considered. Claim 20 has now been amended to provide for "the mammal".

The Examiner contends that claim 2 is not clear in what additional limitation applicants intend by the "pharmaceutically acceptable excipient" of claim 21. Claim 2 has now been amended to provide for a "pharmaceutically acceptable excipient".

Claim Rejections - 35 USC § 112, first paragraph

Claims 1, 2, 4 and 17-24 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. As indicated, the nature of the invention, as claimed, is a method of treating pulmonary disease by administering to the airway of a mammal FoxA2 protein.

The Examiner contends that even if the claims were limited to FoxA2 protein, the specification defines such at page 27 as including "peptides, oligopeptides, and proteins,

including modifications thereof, including amino acid variants and "other modifications", with no requirement for structural identity or conservation as compared to any disclosed particular protein and that, therefore, the breadth of the claims includes treatment of any pulmonary disease by administration of any "FoxA2 therapeutic".

The claims have now been amended to provide for a FoxA2 therapeutic wherein the FoxA2 therapeutic is an isolated, biologically active FoxA2 protein, which is substantially homologous to the native FoxA2 sequence.

Furthermore, the Examiner contends that there is no causality established between the reduction in FoxA2 and any disease or condition. Applicants respectfully disagree with such an assertion. The attached reference "FoxA2 regulates alveolarization and goblet cell hyperplasia" *Development*, 131:953-64 (2004) fully describes the link between FoxA2 protein and lung disease.

The Examiner contends that it would not be predictable that administering the protein extra-cellularly would result in internalization of the protein in active form. To the contrary, this is well established in the art.

While the FoxA2 protein is known in the art to be a transcriptional activating protein, it is well established in the art that such proteins can be administered protein extracellularly and result in internalization of the protein in active form by using short, cationic peptides that cross the plasma membrane efficiently and are known for the use for the intracellular delivery of agents. These peptides are commonly referred to as protein transduction domains (PTDs) and are successfully used to transport heterologous proteins, peptides and other types of products into cells. It is well known to use the membrane transducing technology *in vivo* to deliver biologically active proteins into various tissues.

These peptides are applicable to all cell types (no cell type has yet been described which is not transduced by these PTDs) and the range of cargoes that can be transduced include peptides, small proteins, full-length enzymes, DNA oligomers, peptide-nucleic acid oligomers,

liposomes, and magnetic nanoparticles. See, for example, the attached references: Bogoyevitch et al., DNA and Cell Biology. 2002, 21(12): 879-894; Kabouridis, Biological applications of protein transduction technology Trends in Biotechnology, Volume 21, Issue 11, November 2003, Pages 498-503; and Science 3 September 1999: Vol. 285. no. 5433, pp. 1466 – 1467.

In addition, the Examiner contends that there is an insufficient written description of the invention with respect to the *in vivo* operability of the protein to enable one of ordinary skill in the art to use applicants' invention. Examiner contends that applicant has provided no teaching or guidance indicating what dosages are required and what way(s) the protein can be administered (citing Ex parte Powers, 220 U.S.P.Q. 924 (Bd. Pat. App. & Int. 1982)) or otherwise used in a practical manner and it would, therefore, require undue experimentation of one of ordinary skill in the art to determine how to use the methods, citing Ex parte Forman, 230 U.S.P.Q. 546 (Bd. Pat. App. &Int. 1986).

Applicant respectfully disagrees.

The examiner cited *Ex parte Powers,* 220 USPQ 924 (Bd. Pat. App. Int. 1982), as providing the standard of testing needed to show in vivo efficacy. The examiner apparently concluded that *in vivo* efficacy for the claimed methods must be shown. This basis of the rejection fails to carry the examiner's initial burden of showing nonenablement.

First, the examiner has not provided sufficient evidence to support the position that the claimed methods of treatment are not enabled. See *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971) ("[A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as in compliance with the enabling requirement of the first paragraph of§ 112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support." (emphasis in original)).

The examiner must do more than point to a lack of evidence supporting the breadth of the claims. The burden is not on the applicants to show that the disclosure in the specification is correct; the burden is on the examiner to show that it is not. Pointing out a lack of independent evidentiary support is not enough to carry that burden. "[I]t is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain why it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." *Marzocchi*, 439 F.2d at 224, 169 USPQ at 370. Finally, regardless of what was said in the Board decisions cited by examiner, treatment claims do not necessarily require a showing of in vivo efficacy to be enabled. See, *e.g., Cross v. Iizuka,* 753 F.2d 1040, 1051, 224 USPQ 739, 748 (Fed. Cir. 1985).

Therefore, in light of the submitted amendments and remarks, Applicants respectfully ask that the rejections under 35 U.S.C. 112 be withdrawn.

CONCLUSION

Based on the foregoing amendments and previously filed remarks and Declarations under 37 CFR 1.132, it is submitted that the present application is now in form for allowance. Therefore, early reconsideration and allowance of the claims, as currently pending, are solicited.

The Commissioner for Patents is hereby authorized to charge any deficiency or credit any overpayment of fees to Frost Brown Todd LLC Deposit Account No. 06-2226.

Respectfully submitted,

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